Complete Summary

GUIDELINE TITLE

Anticoagulation - warfarin.

BIBLIOGRAPHIC SOURCE(S)

Singapore Ministry of Health. Anticoagulation - warfarin. Singapore: Singapore Ministry of Health; 2006 Mar. 24 p. [15 references]

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- August 16, 2007, Coumadin (Warfarin): Updates to the labeling for Coumadin to include pharmacogenomics information to explain that people's genetic makeup may influence how they respond to the drug.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

- Venous thromboembolic (VTE) disease
- Atrial fibrillation
- Prosthetic heart valves
- Tissue heart valves
- Myocardial infarction

GUIDELINE CATEGORY

Counseling
Evaluation
Management
Prevention
Risk Assessment
Treatment

CLINICAL SPECIALTY

Cardiology
Family Practice
Hematology
Internal Medicine
Pharmacology
Surgery

INTENDED USERS

Advanced Practice Nurses
Nurses
Pharmacists
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To achieve effective anticoagulation within target international normalized ratio (INR) range
- To reduce complications of anticoagulation therapy
- To improve patient understanding on the safe use of warfarin through patient education

TARGET POPULATION

Patients in Singapore on warfarin anticoagulation therapy

Note: These guidelines have been put together with the Asian population in mind. The workgroup has considered the smaller body weight of the Asian population when recommending the dosing of warfarin.

INTERVENTIONS AND PRACTICES CONSIDERED

1. Use of warfarin for preventing and treating venous and arterial thrombosis and embolism in patients with venous thromboembolic (VTE) disease, atrial fibrillation, prosthetic heart valves, tissue heart valves, or incidence of myocardial infarction
2. Determination and monitoring of warfarin dose
3. Reversal of anticoagulant effects of warfarin in patients going for surgery
4. Management of bleeding and excessive anticoagulation through reduced warfarin dose, increased international normalized ratio (INR) monitoring, admission to hospital, administration of vitamin K or prothrombin complex concentrate supplemented by vitamin K
5. Patient education on the safe use of warfarin

MAJOR OUTCOMES CONSIDERED

- Thromboembolic events
- Incidence of adverse effects including bleeding, skin necrosis, purple toe syndrome, and less serious adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Refer to the "Rating Scheme for the Strength of the Recommendations" for a description of the scheme for rating the strength of evidence and grades of recommendations.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Support Evidence	Implications
1A	Clear	Randomized clinical trials) RCTs without important limitations	Strong recommendation; can apply to most patients in most circumstances without reservation
1B	Clear	RCTs with important limitations (inconsistent results, methodological flaws)	Strong recommendation; likely to apply to most patients
1C+	Clear	No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	RCTs without important	Intermediate-strength

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Support Evidence	Implications
		limitations	recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	RCTs with important limitations (inconsistent results, methodological flaws)	Weak recommendation; alternative approaches likely to be better for some patients under circumstances
2C+	Unclear	No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2C	Unclear	Observational studies	Very weak recommendations; other alternatives may be equally reasonable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Comparison with Guidelines from Other Groups

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The recommendations draw on the proceedings of the Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy and are consistent with most other recently published guidelines such as the Scottish Intercollegiate Guidelines Network's (SIGN) Clinical Practice

Guidelines and the Institute for Clinical Systems Improvement (ICSI) Health Care Guidelines for Anticoagulation Therapy.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions for the strength of the recommendations (1A-2C) are provided at the end of the "Major Recommendations" field.

Indications

Venous Thromboembolic (VTE) Disease

Warfarin therapy should be continued for 6 weeks for patients with symptomatic calf vein thrombosis. Patients with proximal vein thrombosis with a precipitating cause such as surgery or immobilization should receive anticoagulation therapy for 3 to 6 months. Patients with idiopathic proximal vein thrombosis and or pulmonary embolism should receive anticoagulation therapy for at least 6 months **(Grade 1A)**.

Indefinite anticoagulant therapy is indicated for patients with more than one episode of idiopathic proximal vein thrombosis or for those with continuing prothrombotic risk factors **(Grade 1A)** (Ansell et al., 2004; Institute for Clinical Systems Improvement, 2003; Wittkowsky, 1995; Warfarin [drug evaluation monograph]; Hirsch et al., 2003; "Guidelines on oral anticoagulation," 1998)

Atrial Fibrillation

Indefinite anticoagulation therapy is required for prevention of thromboembolic stroke and events **(Grade 1A)**. The benefits must be weighed against the risks. An alternative less effective option with lower risk is the use of anti-platelet drugs. (Ansell et al., 2004; Institute for Clinical Systems Improvement, 2003; Wittkowsky, 1995; Warfarin [drug evaluation monograph]; Hirsch et. al., 2003; "Guidelines on oral anticoagulation," 1998)

Prosthetic Heart Valves

Indefinite anticoagulation therapy is required for prevention of thromboembolic stroke and events **(Grade 1C+)**. (Ansell et al., 2004; Institute for Clinical Systems Improvement, 2003; Wittkowsky, 1995; Warfarin [drug evaluation monograph]; Hirsch et. al., 2003; "Guidelines on oral anticoagulation," 1998)

Tissue Heart Valves

Patients with newly replaced tissue heart valves should receive anticoagulation therapy for 3 months **(Grade 1C)**.

Patients with bioprostheses and atrial fibrillation (AF), previous embolism or severe left ventricular (LV) dysfunction should receive anticoagulants indefinitely **(Grade 1C+)**. (Ansell et al., 2004)

Myocardial Infarction

Lifelong anticoagulation therapy is indicated for:

i. Post-myocardial infarction (MI) patients in persistent AF, lifetime **(Grade 1A)**. The benefits must be weighed against the risks.
ii. Patients with LV thrombus should receive warfarin for at least 3 months **(Grade 2A)**.

(Ansell et al., 2004)

Dosing and Monitoring

General Principles of Warfarin Dosing

1. Loading dose for rapid induction of warfarin should be avoided. Warfarin (irrespective of international normalised ratio [INR]) is not fully effective in the first several days of therapy because of a delayed decrease in several circulating clotting factors. Loading doses can increase a patient's risk of supra-therapeutic INR and make it more difficult to determine a steady-state dose.
2. The target INR for most conditions is 2 to 3. However, this range should be adjusted according to the bleeding and thrombotic risks of each individual.
3. While there is a significant increase in thromboembolism as INR values decrease below 1.7, the bleeding risk increases substantially at INR above 5. Clinical risk and past medical history should be considered in all dosing decisions.
4. Prescription and over-the-counter medications can adversely affect the INR response to warfarin. Herbal or natural remedies can change the INR response to warfarin and/or increase a patient's risk of bleeding. In these instances, additional monitoring may be needed. Please refer to table 7.1 and 7.2 in the original guideline document for the drug-drug and drug-herb interactions respectively.
5. Food that contains moderate amounts of vitamin K can decrease the INR response to warfarin. Patients should maintain a consistent diet. Please refer to table 7.3 in the original guideline document for the vitamin K content in common foods.

Initiation and Maintenance of Warfarin Therapy

1. For patients with ongoing thrombosis, warfarin should be started concomitantly with low molecular weight heparin or standard heparin. Patients without active thrombosis but who require warfarin for prophylactic indications, e.g., atrial fibrillation, can be initiated on warfarin alone.
2. Patients receiving warfarin for the first time should begin with 2 mg to 5 mg daily.

3. Lower warfarin doses should be considered for patients with any of the following factors:
    i. Age greater than 75 years
    ii. Multiple co-morbid conditions
    iii. Low albumin levels and poor nutritional status
    iv. Impaired liver function, cardiac function and thyroid function

(Please refer to table 7.4 in the original guideline document for endogenous interactions with warfarin)

4. A baseline INR value should be drawn to rule out any underlying coagulopathy.
5. Monitoring of INR can be done at inpatient or outpatient settings.
6. During the first week, INR should be measured daily or every other day and warfarin dosage adjusted accordingly. It is then measured at increasing intervals, depending on the INR response.
7. Once the warfarin dose is stable, many patients can be well controlled with 4 to 8 weekly INR testing and warfarin dose adjustments. Steady-state INR values will not be realized for up to 3 weeks following a dose adjustment.
8. Patients with INR values outside target INR range should be considered for more frequent monitoring. Those with INR less than 1.5 or above 4 should have their INR repeated within seven days following dose adjustments.
9. Warfarin maintenance dose is usually in the range of 2 mg to 10 mg orally once a day.
10. Warfarin dosing is affected by numerous factors. These are tabulated in table 7.5 in the original guideline document. An assessment of clinical variables known to affect the INR should be made with each dose adjustment.

Reversing Anticoagulant Effects of Warfarin in Patients Going for Surgery

1. For elective procedures, warfarin should be stopped 3 to 5 days prior to surgery.
2. Patients with INRs of between 2 to 2.5 should achieve an INR of less than 1.5 after stopping warfarin for 3 days. Patients with INRs of between 2.5 to 3.5 generally require discontinuation of warfarin for 4 days before their INRs will drop to less than 1.5.
3. INR should be checked just before surgery to ensure adequate haemostatic function.
4. Warfarin may be restarted 24 hours after surgery if there is no bleeding risk.
5. The need to use heparin or low molecular weight heparin during the perioperative period should be considered based on the bleeding risk from the surgery as well as the thrombotic risk arising from the surgery and the duration that the patient has to come off warfarin. This should be reviewed by the physician in charge.

Managing Bleeding and Excessive Anticoagulation

The Risk of Bleeding and INR

Bleeding risk increases significantly when INR exceeds 5. An INR above 5 requires close monitoring. Intervention is required based on the INR reading, the presence of bleeding and the patient's underlying condition, as outlined.

The Recommendation for Management if There is No Significant Bleeding and Patient has Low Bleeding Risks

INR	Recommendation
4.0 to 5.0	Reduce dose or omit 1 to 2 doses. Monitor international normalised ratio (INR) more frequently and resume therapy at a lower dose when INR is within therapeutic range.
5.0 to 9.0	Check for bleeding/headache/anaemia. Admit if any suspicion of bleeding or if patient is unwell. If not for admission, advise patient of risk of bleeding and to go to accident and emergency (A & E) if there is any suspicion of bleeding or if patient is unwell. Omit 2 to 3 doses. Monitor INR more frequently and resume therapy at a lower dose when INR is within therapeutic range. Alternatively, omit 1 dose and administer 1 mg to 3 mg of oral vitamin K. Check INR in 24 hours. If INR remains high, administer additional 1 mg to 2 mg of oral vitamin K. Resume therapy at a lower dose when INR is within therapeutic range.
Above 9.0	Admit. Check for bleeding/headache/anaemia. Omit warfarin and administer 3 mg to 5 mg of oral vitamin K. Check INR in 24 hours. Administer additional vitamin K if necessary. Resume therapy at a lower dose when INR is within therapeutic range.

The Recommendation for Management if There is Serious Bleeding and INR is Elevated

Hold warfarin therapy and administer 10 mg vitamin K by slow intravenous (IV) infusion, supplemented with fresh plasma or prothrombin complex concentrate 50 IU/kg, depending on the urgency of the situation. Vitamin K administration can be repeated every 12 hours.

For life-threatening bleed, hold warfarin therapy and administer prothrombin complex concentrate 50 IU/kg, supplemented with 10 mg vitamin K by slow IV infusion. Check INR every 6 hours and repeat the procedure if necessary, depending on the INR.

Oral vitamin K is given for outpatients. The oral preparation is prepared from KONAKION MM® preparation. IV Konakion® has oral bioavailability of 50% (Roche company data).

Considerations for Vitamin K

The dose of vitamin K used to reverse over-anticoagulation depends on the INR. Ideally, vitamin K should be administered in a dose that will quickly lower INR into a safe but not sub-therapeutic range. For most patients, 1 mg to 3 mg of vitamin K is sufficient in the absence of bleeding. These small doses are obtained by dilutions from a 10 mg vial of injectable vitamin K and this is administered via oral or parental route.

High doses of vitamin K (10 mg) are very effective but will lower the INR to sub-therapeutic range and lead to warfarin resistance for up to a week.

Due to near complete absorption, oral vitamin K has shown to be convenient and effective.

Intravenous injection produces a rapid response but anaphylactic reaction is a rare complication. This is reserved for patients who require very rapid reversal of anticoagulation; and can be administered by slow intravenous infusion (10 mg over 30 minutes in 50 mL dextrose 5%).

Warfarin Counselling

See the original guideline document for Frequently Asked Questions during Warfarin Counselling.

Definitions:

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Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Support Evidence	Implications
			stronger evidence is available
2A	Unclear	RCTs without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
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CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Optimal management of warfarin therapy for prevention and treatment of venous and arterial thrombosis and embolism in patients with venous thromboembolic (VTE) disease, atrial fibrillation, prosthetic heart valves, tissue heart valves, or incidence of myocardial infarction
- Prevention of adverse effects caused by warfarin therapy
- Optimal management of bleeding and excessive anticoagulation caused by warfarin therapy

POTENTIAL HARMS

Adverse Effects

Bleeding

The most common adverse effect of warfarin is bleeding with reported rates of major bleeding between 1.1% and 8.1% during each year of long term warfarin treatment. Although the risk of bleeding for patients on warfarin increases substantially at international normalised ratio (INR) values greater than 5, bleeding can occur at any INR value. The use of warfarin often unmasks bleeding potential e.g., a non bleeding peptic ulcer may bleed if the patient is put on warfarin.

The risk of bleeding is additive and related to the intensity of anticoagulation, use of concurrent medications and the patient's clinical condition.

Risk Factors for Bleeding During Warfarin Therapy

Patient Related	
Age:	Above 65 years old
Cardiac:	Recent myocardial infarction (MI), atrial fibrillation (AF), severe hypertension (diastolic pressure >100 mmHg, systolic pressure >180 mmHg)
Gastrointestinal:	Active peptic ulcer disease, history of gastrointestinal bleeding, hepatic insufficiency
Hematologic/oncologic:	Anaemia, thrombocytopenia, platelet dysfunction, coagulation defect, malignancy
Neurologic:	History of stroke, dementia, cognitive or psychological impairment

Medications:	Use of other medications, such as non-steroidal anti-inflammatory drugs (NSAIDS), or "natural remedies" that interfere with haemostasis
Others:	Recent trauma or surgery, excessive alcohol intake, intramuscular injection, potential bleeding sites (lumbar puncture, biopsy site, intra-arterial puncture)

Skin Necrosis

Skin necrosis is associated with thrombosis of venules and capillaries within subcutaneous fat, and usually occurs within the 3rd to 8th day of treatment. It presents as painful localised skin lesions and is usually associated with protein C or S deficiency. Skin necrosis may occur with large loading doses of warfarin and may be circumvented by initiating therapy at low doses while continuing heparin to avoid an abrupt fall in protein C levels before coagulation factor levels are reduced.

Purple Toe Syndrome

Purple toe syndrome is characterized as a dark cutaneous lesion with blue discoloration of the feet and lower leg. It is caused by peripheral emboli and usually occurs 3 weeks to 10 weeks after initiation of therapy.

Less Serious Adverse Effects

Adverse effects that are less serious include alopecia, osteoporosis, rash and gastrointestinal discomfort.

Considerations for Vitamin K

High doses of vitamin K (10 mg) are very effective but will lower the international normalized ratios (INR) to sub-therapeutic range and lead to warfarin resistance for up to a week. Intravenous vitamin K injection produces a rapid response but anaphylactic reaction is a rare complication.

CONTRAINDICATIONS

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Anticoagulation therapy is contraindicated in any medical condition or personal circumstance in which the risk of haemorrhage is greater than the potential clinical benefits of anticoagulation.

Haemorrhage

Warfarin is contraindicated for patients with active haemorrhage, cerebral vascular haemorrhage (confirmed or suspected) and those with active bleeding disorder and bleeding lesions of the gastrointestinal, respiratory and urinary tracts.

Pregnancy

Warfarin crosses the placenta and foetal exposure to warfarin is associated with a characteristic embryopathy, central nervous system (CNS) abnormalities, foetal bleeding and increased foetal loss. The incidence of warfarin embryopathy is greatest at 6 weeks to 12 weeks of gestation. Warfarin also increases the risk of serious perinatal bleeding during delivery.

Warfarin should be avoided throughout the entire pregnancy especially during the first and third trimester.

Breast-feeding

Warfarin does not induce an anticoagulant effect in the breast-fed infant and is therefore not contraindicated for the nursing mother.

Miscellaneous

- Hypersensitivity to warfarin or any component
- Severe uncontrolled hypertension
- Severe vasculitis
- Recent (2 weeks to 3 weeks) trauma (especially to the central nervous system)
- Neurosurgical procedures
- Aneurysms (cerebral or dissecting)
- Blood dyscrasias associated with haemorrhage or thrombocytopenia

Caution is to be exercised if there is debility of any cause, dysfunction from primary or secondary hepatic disorders, and conditions associated with vitamin K deficiency.

QUALIFYING STATEMENTS

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The contents of this publication are guidelines for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each healthcare professional is ultimately responsible for the management of his/her unique patient in the light of clinical data presented by the patient and the diagnostic and treatment options available.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Singapore Ministry of Health. Anticoagulation - warfarin. Singapore: Singapore Ministry of Health; 2006 Mar. 24 p. [15 references]

ADAPTATION

The recommendations draw on the proceedings of the Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy.

DATE RELEASED

2006 Mar

GUIDELINE DEVELOPER(S)

Singapore Ministry of Health - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

Singapore Ministry of Health

GUIDELINE COMMITTEE

Workgroup on Anticoagulation - Warfarin

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

ENDORSER(S)

Pharmaceutical Society of Singapore - Medical Specialty Society
Singapore Society of Haematology - Medical Specialty Society

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Singapore Ministry of Health Web site.

Print copies: Available from the Singapore Ministry of Health, College of Medicine Building, Mezzanine Floor 16 College Rd, Singapore 169854.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on April 2, 2008. The information was verified by the guideline developer on May 12, 2008.

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